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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,004	SAH ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *1-6,11-14,18,19 and 21-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10, 15-17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1705
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 06/01/2007.

Election/Restrictions

2. Applicant's election with traverse of group 311, SEQ ID No. 471, claims 16-17 in the reply filed on 06/01/2007 is acknowledged. The traversal submitted on 02/26/2007 is on the ground(s) that that the MPEP section 803.04 instructs examiners to search up to 10 nucleotide sequences per application and groups CCCX1-CCCXX recite only ten nucleotides sequences and therefore these groups should be searched and examined. The response further asserts that six of these sequences are duplicates and pose no additional search burden on the examiner. This is not found persuasive because the office rescinded the 1996 waiver of permitting up to ten independent and distinct polynucleotides published in the O.G. notice on March 27, 2007 based upon the increasing computational, search, and examination burden required for the consideration of nucleic acid sequences and complexity of claims drawn to such, compared to the time of the 1996 waiver. Furthermore, applicant did not elect any of the six sequences that are duplicate and therefore the sequence that is examined is SEQ ID No. 471.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-6, 11-14, 18-19, 21-66 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 02/26/2007 and 06/01/2007.

4. Claims 7-10, 15-17 and 20, SEQ ID No. 471 are under examination.

Drawings

5. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 7-10, 15-17 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The nature of the claims is drawn to evaluating the level of neuropathic pain in a mammal by analyzing the amount of a nucleic acid in skin biopsy sample under conditions of neuropathic pain compared to a second skin biopsy sample under conditions of substantially no neuropathic pain. The claims are further drawn to difference in 2-fold amount of nucleic acid in the first sample compared to second samples. The claims are further drawn to samples from the same mammal. The claims are further drawn to rodent and human. The claims are further limited to the nucleic comprises a nonredunant sequence of SEQ ID No. 471 and the surrogate maker is muscle-specific.

The rejected claims encompass analysis of any mammal, including human and non-human mammals. The rejected claimed encompass analysis of any nucleic acid, any difference in the amount of nucleic acid, increase or decrease, and any level of neuropathic pain.

The nature of the claims requires knowledge of a correlation between any nucleic acid expression and detection of any level of neuropathic pain in any mammal.

Guidance in the Specification and Working Examples

The specification asserts a method for determining neuropathic pain from obtaining a skin biopsy sample and determining the gene expression levels measured in the skin punch biopsy samples (see paragraph 5 and paragraph 6).

The specification asserts that a difference between the amount of nucleic acid in the first sample and the amount of nucleic acid in the second sample indicates that the nucleic acid is a surrogate marker of neuropathic pain. However the claims are broadly drawn to any amount of

nucleic acid, increase or decrease as well as any level of neuorapathic pain and the specification does not teach predictably correlating any expression level with any level of neuropathic pain.

The specification asserts that SEQID No. 471, is in group III, category SMP, and is associated with NM_006063.1 (see table 4). However, the specification does not give any data, expression level, any skin biopsy results of SEQ ID No. 471 or any nonredunant subsequence of SEQ ID No. 471. Furthermore, SEQ ID No. 471 is a human DNA sequence and the specification does not teach any studies, obtaining skin biopsies or working examples of a gene expression analysis of neuropathic pain in humans.

The specification demonstrates a working example of obtaining skin samples from rats post-spinal nerve ligation and analysis of mRNA from skin biopsies profiled on Affymetrix Rat Genome arrays (See examples). However the specification does not demonstrate that the expression levels are predictably correlative to an increase or decrease level of neuropathic pain. The specification does not demonstrate the amount of neuropathic pain that is associated with the gene expression obtained from the skin biopsies. Furthermore, the data presented in the specification does not predictably correlate any neuropathic pain with an increase in expression, as different neuropathic pains result in different gene expression values in rats (see figure 1, 2, for example).

The specification does not teach a control study, a predictive value, nor a connection between the expressed gene and the neuropathic pain level in either humans or rats. The specification does not teach the "any" type of mammal. The specification does not provide any guidance with the status of the neuropathic pain, for example did the rats have any other diseases that would affect the condition of the skin (for example, diabetes) and possibly affect the gene

expression level of the marker genes? Based on the teachings in the specification, it is unclear how the expression level of any nucleic acid level would determine the level of neuropathic pain in any mammal.

It is unclear how the skilled artisan would be able to determine the level of neuropathic pain because the specification does not teach which genes are correlative with levels of neuropathic pain in a skin biopsy in any mammal, rodent or human.

The following is unclear from the teaching in the specification. The specification does not teach the analysis of "any" level of neuropathic pain, in "any" mammal by obtaining a skin biopsy and determining the level of "any" nucleic acid. The specification provides no teaching of how the level of neuropathic pain is correlative to gene expression.

The specification envisions hypothetical situations where "any" neuropathic pain level can be determined by any expression level of a nucleic acid in a mammal. The specification appears to be conceiving of possible scenarios where the expression level could be determined in a skin biopsy and that these levels could indicate neuropathic pain levels, however, it is unclear how one of skill in the art would determine the level of expression necessary to determine the ability to predictably correlate the level of neuropathic pain level based on the expression level of a nucleic acid.

The unpredictability of the art and the state of the prior art

While the state of the art and level of skill in the art with regard to detection of a gene expression in a biological sample is high, the level of unpredictability in associating any particular expression level of a gene with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art teaches that there are many parameters that need to be evaluated prior to using gene expression as a test to determine the level of neuropathic pain in any mammal. Furthermore, the prior art teaches that the parameters that need to be addressed in order to conduct a study on modulating gene expression yield gaps in information that are needed to complete a thorough screening of gene expression effects.

Shalon et al. (US 2001/0051344 A1 Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph 0155). Shalon et al. further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph 0156). Sharlon et al. teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph 0158). Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a

particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph).

Additionally, the prior art teaches the unpredictability of determining neuropathic pain within different species of rats, which further demonstrates the unpredictability of extrapolating the data from rats to human. Lovell et al. (Pharm. Biochem. and Behavoir, 2000, vol. 65:141-144) teach strain-related differences in thermal hyperalgesic response to peripheral nerve injury in rats (see pg. 143, 2nd column, last paragraph). Lovell et al. teach the mechanisms underlying strain difference in behavioral hypersensitivity to thermal nociceptive stimuli are less than clear (see pg. 144, 1st column, last paragraph). Furthermore, Benoliel et al. (Pain 20002, 97:203-212)

demonstrate that different strains of rats have different pain tolerances. Benoliel et al. demonstrate that the effect of strains on the extent of measurable behavior parameters have been greatly studied and demonstrate that Lewis rats developed hyerpalgesic responses slower than Sprague-Dawly rats (see pg. 210, last column, last para. con't to next page). Benoliel et al. demonstrate that Sprague Dawly rates and Lewis rats, will vary in response to pain. Therefore, the prior art teaches the unpredictability of neuropathic pain levels among the same species and demonstrates the unpredictability of extrapolating neuropathic pain levels among different mammal species.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to correletation of any level of expression of a nucleic acid in skin biopsy with the level of neuropathic pain in any mammal, the quantity of experimentation in this area is extremely large. The skilled artisan would have to determine a predictable correlation between any nucleic acid molecule, including the nonredundant subsequence of SEQ ID no. 471, that would be capable of detecting and determining the level of neuropathic pain in all mammal species. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine a gene expression profile in many different mammals with many different types of neuropathic pain and pain levels and then determine if each genes expression profile is changed upon the level and type of neuropathic pain. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if the gene is in fact detecting neuropathic pain. There is

still a significant amount of unpredictably in identifying genes and within the human gene, a skilled artisan would be unable to know if the detected sequence was detecting neuropathic pain and the skilled artisan after detection of the sequence would have to perform a large exhaustive assay to test for gene detection in large study pool to determine the specific genes that identify only neuropathic pain and pain levels . This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the lack of guidance on how to predictably correlate gene expression with neuropathic pain levels in any mammal, the large quantity of research required to define the lack of guidance provided in the specification, the absence of working examples, and the negative teaching in the prior art balanced only against the high level of skill in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 7, 9, 15, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Terenghi et al. (cited on IDS).

Terenghi et al. teach obtaining skin calf biopsies from six diabetic and six control

Patients (see pg. 34, 1st column, 2nd full paragraph). Terenghi et al. teach an increase in TrkA (muscle specific, claim 20) mRNA expression compared to normal control (see figure 2). Terenghi et al. teach the first and both sets of skin biopsy samples are obtained from humans (see pg. 34, 1st column, 2nd full paragraph) (claims 9 and 15).

9. Claims 7-9, 15 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Diemel et al. (Diabetic Medicine, 1999, vol. 16, pp. 113-118, cited on IDS).

Diemel et al. teach measuring mRNA expression level of NGF (claim 20, muscle specific) in skin biopsies of 19 diabetic patient compared with samples from eight controls (see abstract). Diemel et al. teach an increase in 4 to 14 fold mRNA expression in diabetic patients (See figure 1) (claim 8). Diemel et al. teach the first and second samples were obtained from humans (claim 9 and 15) (see pg. 114, 1st column, last paragraph). Diemel et al. teach that the increase in NGF indicates the level of neuropathic pain (see pg. 117, table 1, 1st column, 2nd paragraph, and abstract).

Conclusion

10. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Sarae Bausch, PhD.
Examiner
Art Unit 1634